UNITED STATES OF AMERICA
BEFORE THE FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

In the Matter of: **Enrofloxacin for Poultry: Withdrawal of Approval of New Animal Drug Application NADA 140-828**	**FDA DOCKET: 00N-1571**

RESPONDENT BAYER CORPORATION'S
MOTION TO REFORMULATE ISSUES FOR HEARING

RESPONDENT Bayer Corporation, holder of the new animal drug application (NADA 140-828) that is the subject of the above-referenced Notice of Hearing ("NOH"), hereby moves to modify the issues for hearing set forth by the Commissioner in the NOH, 67 Fed. Reg. 7700, 7701 (Feb. 20, 2002), to read as follows:

> Whether new evidence shows that enrofloxacin is not now shown to be safe for use under the conditions of use upon which the application was approved. This issue includes:
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> A. Whether CVM has presented new evidence that raises serious questions about the safety of enrofloxacin. Specifically:
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> 1. Whether CVM has presented new evidence that the use of enrofloxacin in chickens causes significant fluoroquinolone-resistant Campylobacter spp. in chicken meat consumed by humans;
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> 2. Whether CVM has presented new evidence that fluoroquinolone-resistant Campylobacter spp. in chickens caused by the use of enrofloxacin in chickens are transferred to humans and are a significant cause of fluoroquinolone-resistant Campylobacter infections in humans; and

3. Whether CVM has presented new evidence that fluoroquinolone-resistant Campylobacter infections in humans caused by the use of enrofloxacin in chickens pose a greater potential hazard to public health than was anticipated when the drug was approved.

4. Whether CVM has presented new evidence that the use of enrofloxacin in turkeys causes significant fluoroquinolone-resistant Campylobacter spp. in turkey meat consumed by humans;

5. Whether CVM has presented new evidence that fluoroquinolone-resistant Campylobacter spp. in turkeys caused by the use of enrofloxacin in turkeys are transferred to humans and are a significant cause of fluoroquinolone-resistant Campylobacter infections in humans; and

6. Whether CVM has presented new evidence that fluoroquinolone-resistant Campylobacter infections in humans caused by the use of enrofloxacin in turkeys pose a greater potential hazard to public health than was anticipated when the drug was approved.

B. If such new evidence has been shown,

1. Whether the benefits of continued enrofloxacin use in chickens under the current recommended or suggested conditions of use in the labeling or under some alternative pattern of restricted use outweigh the risks/costs of such continued use, such that enrofloxacin is safe. This analysis will include consideration of impacts on (a) human health, (b) animal health, (c) the environment, and (d) the economy; and

2. Whether the benefits of continued enrofloxacin use in turkeys under the current recommended or suggested conditions of use in the labeling or under some alternative pattern of restricted use outweigh the risks/costs of such continued use, such that enrofloxacin is safe. This analysis will include consideration of impacts on (a) human health, (b) animal health, (c) the environment, and (d) the economy.

In support of its motion, Bayer states as follows:

INTRODUCTION

This motion addresses three deficiencies in the Food and Drug Administration's ("FDA") issues for hearing. First, the issues formulated by FDA do not accurately reflect the parties' burdens of proof and the legal standards governing the hearing. There is no dispute that FDA has the initial burden of coming forward with new evidence that raises serious questions about the safety of enrofloxacin. The issues as drafted by FDA, however, do not reflect that burden. FDA's issues do not reflect the requirement that new evidence *show* that there are *serious* questions about the safety of enrofloxacin use in chickens and turkeys. The issues framed by FDA would effectively lower the bar to allow the agency merely to infer the existence of theoretical questions about the safety of enrofloxacin use and shift the burden to Bayer. The proper standard requires FDA to come forward with new evidence that demonstrates ("shows") that there is a reasonable basis seriously to question enrofloxacin's safety.

Second, FDA's formulation of the issues inadequately addresses how the "safety" of enrofloxacin is to be determined. The D.C. Circuit has held repeatedly that in determining whether a drug is "safe," FDA is required to consider the relative risks and benefits of the drug. The issues framed by FDA merely ask whether enrofloxacin is "safe," without providing any guidance at all as to how "safety" shall be assessed. Accordingly, Bayer moves to reformulate the issues so that they reflect the appropriate standard.

Finally, FDA's issues as framed call for an analysis of the "safety" of enrofloxacin in *all poultry*. Enrofloxacin is not approved for use in "poultry." It has separate label

approvals for use in chickens and turkeys. The Notice of Opportunity for Hearing ("NOOH"), however, focused on evidence that is said to call into question the safety of enrofloxacin as used in *chicken*. Enrofloxacin is also used in turkeys, but the NOOH offered no findings to suggest that FDA has reason to believe that enrofloxacin is unsafe for use in turkeys. Without any such evidence, there is no basis for withdrawing approval for the use of enrofloxacin in turkeys. Under FDA's issues, however, a finding that enrofloxacin is "unsafe" as used in chickens would require its withdrawal from all uses. The issues for hearing should be reframed so that the safety of enrofloxacin will be assessed separately for chickens and for turkeys.

Bayer proposes the revisions to FDA's formulation of issues discussed below to more accurately reflect the parties' respective burdens of proof and the applicable legal standard for this proceeding. The issues are identified in the format and numbers assigned to them in the notice of hearing in the Federal Register. 67 Fed. Reg. at 7700.

I. FDA's PROPOSED ISSUES DO NOT PROPERLY REFLECT THE "NEW EVIDENCE" REQUIREMENT AND DO NOT PROPERLY DESCRIBE FDA's STATUTORY BURDENS.

In the NOOH, FDA proposed to withdraw approval of NADA 140-828 for use in poultry pursuant to Section 512(e)(1)(B) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), which states:

> (e)(1) The Secretary shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an application filed pursuant to subsection (b) with respect to any new animal drug if the Secretary finds—
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> * * * *
>
> (B) That new evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was

> approved, evaluated together with the evidence available to the secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved or that subparagraph (I) of paragraph (1) of subsection (d) applies to such drug.

21 U.S.C. § 360b(e)(1)(B).

Under the governing provisions of the FDCA, the initial question is whether there is *new evidence*. The next question is whether the new evidence "shows" that there are serious questions about the ultimate safety of enrofloxacin. Because FDA's formulation of the issues for hearing does not accurately reflect the "new evidence" requirement and the requirement that the new evidence demonstrate the existence of serious questions regarding safety, the issues should be modified.

A. FDA Has the Initial Burden of Producing New Evidence That Shows There Are Serious Questions About the Safety of Enrofloxacin, and the Issues Must Reflect This Burden.

Issue A

This issue now reads as follows:

> A. Whether there is a reasonable basis from which serious questions about the safety of enrofloxacin use in poultry may be inferred, such as:
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> * * * *

Bayer Proposed Issue A

Bayer proposes that this issue be rephrased as follows:

> A. Whether CVM has presented new evidence that raises serious questions about the safety of enrofloxacin. Specifically:
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> * * * *

FDA's formulation of Issue A is flawed because it does not reflect FDA's statutory burden to present "new evidence" that "shows" that enrofloxacin is no longer shown to be

safe. Bayer's proposed Issue A clarifies the standard by explicitly linking the "new evidence" standard with what that new evidence must show.

Moreover, the issue as framed by FDA sets the agency's burden of proof too low. The NOH states that FDA:

> [M]ust provide a reasonable basis from which serious questions about the ultimate safety of the drug may be inferred . . . Once [FDA] provides a basis for questioning the safety of enrofloxacin, the sponsor will have the ultimate burden of showing the drug's safety.

67 Fed. Reg. at 7700. FDA further asserts that these serious questions "can be raised where the evidence is not conclusive, but merely suggestive of an adverse effect." *Id.* While the general notion that the burden of proof shifts to Bayer once FDA provides a reasonable basis for seriously questioning the safety of enrofloxacin is correct, FDA's formulation would allow the burden to shift before the agency has made a sufficient showing. The D.C. Circuit has rejected FDA's position.

The statute plainly requires FDA to come forward with new evidence that "shows" that an approved drug is not now shown to be safe for its intended use before such an approval may be withdrawn. 21 U.S.C. § 360b(e)(1)(B). FDA asserts that the D.C. Circuit, in *Rhone-Poulenc, Inc. v. FDA*, 636 F.2d 750 (D.C. Cir. 1980), affirmed a standard that permits FDA to discharge its burden of proof with evidence that is "merely suggestive." *See* 65 Fed. Reg. 64,954, 64,955 (Oct. 31, 2000). To the contrary, the D.C. Circuit in *Rhone-Poulenc* made clear that the agency may not "infer" questions:

> We must therefore review the record in this case to determine whether the FDA has presented new evidence raising questions about the safety of [the drug] that are *sufficiently serious* to require the manufacturers to demonstrate that [the drug] is safe.

Rhone-Poulenc, 636 F.2d at 752 (emphasis added). Thus, evidence that is "merely suggestive" or that raises the mere inference of a question regarding safety will not satisfy FDA's burden. The issue posed by FDA should be reformulated to reflect accurately the proper burden of proof.

B. FDA's Proposed Subissues Do Not Pose Questions That Bear Any Relevance to the Proper Statutory Standards and Required Burdens of Proof.

Subissue A (1)

This subissue now reads as follows:

> 1. Whether enrofloxacin use in poultry acts as a selection pressure, resulting in the emergence and dissemination of fluoroquinolone-resistance *Campylobacter* spp. in poultry?

Bayer Proposed Subissue A (1)

Bayer proposes that this subissue be rephrased as follows:

> 1. Whether CVM has presented new evidence that the use of enrofloxacin in chickens causes significant fluoroquinolone-resistant *Campylobacter* spp. in chicken meat consumed by humans.

Bayer proposes this revision of Subissue A (1) because FDA's formulation of the subissue poses a question that is not probative on the ultimate issue of safety. First, as described above, FDA's burden of proof requires it to adduce "new evidence." Further, the subissue as drafted fails to require any evidence of the significance or extent of selection pressure. Bayer does not dispute the scientific principle that use of any antibiotic in man or animal can exert a selection pressure, which, if substantial enough, could have the effect of eliminating susceptible microbes, leaving a resistant population of microorganisms. The record clearly shows that FDA was well aware, prior to the approval of enrofloxacin, of this general principle of population biology. FDA was also aware at

that time of the very rapid development of resistance of *Campylobacter* to the older quinolones as well as to the newer fluoroquinolones, and also aware that the use of fluoroquinolones in poultry exerts a selection pressure to produce *Campylobacter* with decreased susceptibilities and resistance.

The crux of the issue is *to what extent* the use of enrofloxacin in chickens and/or turkeys acts as a selection pressure beyond that already known at the time of approval, the significance of that fact, and whether FDA has new evidence that demonstrates this significance. In *Hess & Clark v. FDA*, 495 F.2d 975 (D.C. Cir. 1974), for example, the court rejected the argument that FDA had met its burden in connection with a proposed withdrawal of a drug approval for DES by showing that animal carcasses contained DES residues and that DES was a carcinogen. *Id.* at 992. The court required a showing by FDA that the detected residues were related to the use of DES implants. Likewise, here, it is not sufficient for FDA to merely show that selection pressure exists. FDA must demonstrate (with evidence not available at the time of approval) that enrofloxacin actually exerts sufficient selection pressure to produce an adverse effect on human health. To pose the question as FDA has formulated it will result in an answer that does not bear on the ultimate issue of the hearing—whether FDA has new evidence that enrofloxacin is not now shown to be safe.

FDA implicitly acknowledges the relevance of the issue of the extent or significance of selection pressure. In the NOH the agency states, "CVM has concluded . . . that the use of fluoroquinolones in poultry is a *significant* cause of fluoroquinolone-resistant *Campylobacter* on poultry carcasses. . . ." 67 Fed. Reg. at 7700 (emphasis added). FDA cannot meet its burden of proof without evidence to support this conclusion.

The rate of usage of enrofloxacin in the United States chicken broiler population is extremely small, at approximately 1% or less. Therefore, the overwhelming majority of the approximately 21 billion pounds of chicken consumed annually by the American public has never been treated with enrofloxacin. Furthermore, data from surveillance programs, and other sources, also show that both the prevalence and pathogen load of chickens colonized with *Campylobacter* is decreasing due to HACCP[1] and other factors. Additionally, data from the National Antimicrobial Resistance Monitoring System ("NARMS") demonstrate that the rate of fluoroquinolone-resistant *Campylobacter jejuni* in U.S. poultry has remained stable since 1998, the period when NARMS first started to collect *Campylobacter* isolates from poultry. Thus, FDA must provide new evidence that, despite minimal usage, decreasing *Campylobacter* loads, and stable fluoroquinolone resistance rates in *Campylobacter*, enrofloxacin use is causing resistance at a level beyond what was anticipated at the time of approval and at a level that has some significance to human health.

The scientific principle of selection pressure is itself not a binary issue, subject to a yes or no answer. Selection pressure varies based on a variety of factors. FDA itself has stated that "[s]election will depend upon the type of antimicrobial used, the number of individuals treated, the dosage regimen, and the duration of treatment." Judicious Use of Antimicrobials for Poultry Veterinarians, Center for Veterinary Medicine (G-113). Any increase or decrease in these factors will affect the rate of selection pressure. It is this *rate* that is at issue. Whether selection pressure exists is not in dispute.

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[1] HACCP is the Hazard Analysis and Critical Control Point system adopted in 1998 by the U.S. Department of Agriculture for meat and poultry processing plants. It is designed as a process control system that can be used to prevent hazards to the food supply and a tool in the control, reduction, and prevention of

The evidence also shows that enrofloxacin is not the only selection pressure that acts upon *Campylobacter*. Fluoroquinolone-resistant *Campylobacter* are naturally present in the environment and are found in poultry even where flocks have not been treated with fluoroquinolones. *Campylobacter* are ubiquitous in the environment and colonize pets such as dogs and cats as well as domesticated and wild mammals, birds, flies and other animals. It is widely acknowledged that the extensive use of fluoroquinolones to treat illness in people acts as a major selection pressure on the development of fluoroquinolone-resistant *Campylobacter* and other bacteria. It was shown many years ago that selection pressure can result from other sources including detergents, biocides, and other antimicrobials. Since enrofloxacin is not the only selection pressure exerted on *Campylobacter*, FDA must consider these other factors when evaluating enrofloxacin's impact.

All of these facts demonstrate that whether selection pressure exists is not the issue. Bayer does not dispute the theory of selection pressure. Rather, the issue is to what extent the use of enrofloxacin acts as a selection pressure, what significance selection pressure has on the rest of the purported causal link to adverse human health effects, and what new evidence FDA has that demonstrates this significance. Bayer has recast Subissue A (1) to pose the real issue: "[w]hether CVM has presented new evidence that the use of enrofloxacin in chickens causes significant fluoroquinolone-resistant *Campylobacter* spp. in chicken meat consumed by humans."

Subissue A (2)

This subissue now reads as follows:

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pathogens in meat and poultry. Since the introduction of HACCP, pathogen loads on meat and poultry continue to decrease significantly.

2. Whether fluoroquinolone-resistant *Campylobacter* spp. in poultry are transferred to humans and whether they contribute to fluoroquinolone-resistant *Campylobacter* infections in humans.

Bayer Proposed Subissue A (2)

Bayer proposes that this subissue be rephrased as follows:

2. Whether CVM has presented new evidence that fluoroquinolone-resistant *Campylobacter* spp. in chickens caused by the use of enrofloxacin in chickens are transferred to humans and are a significant cause of fluoroquinolone-resistant *Campylobacter* infections in humans . . . .

FDA's formulation of Subissue A (2) contains the same fatal flaws described above. FDA's question as posed, even if answered affirmatively, sheds no light on the ultimate issue—the impact, if any, of chicken and/or turkey enrofloxacin use on human health. FDA's burden of proof requires it to adduce "new evidence," and that evidence must demonstrate the significance of any transfer of fluoroquinolone-resistant *Campylobacter* from chickens and/or turkeys to humans as it relates to enrofloxacin. FDA implicitly acknowledges the relevance of evidence bearing on fluoroquinolones' significance as a cause of resistant *Campylobacter* infections in humans. In the NOH, the agency states: "CVM has concluded . . . that the use of fluoroquinolones in poultry is . . . a *significant* cause of fluoroquinolone-resistant *Campylobacter* infections in humans." 67 Fed. Reg. at 7700 (emphasis added).

The record is replete with evidence that demonstrates that *Campylobacter* spp. (both resistant and susceptible to antimicrobials) harbored in many species of animals can be transferred to humans. The record shows that this evidence was well-understood by FDA years prior to the approval of enrofloxacin. Yet FDA's formulation of the issue ignores its burden to come forward with new evidence—evidence not known at the time it approved enrofloxacin—showing chicken as a pathway for *Campylobacter* and

demonstrating that the rate of fluoroquinolone-resistant infections is more than minimal (and more than anticipated at the time of approval), such that it bears on the ultimate issue of safety of the product.

FDA's formulation of this issue sets the bar too low. The mere fact that such transfer *can* occur does not mean that such transfer *is* occurring to any degree (or to a greater degree than anticipated) that affects human health or the safety of enrofloxacin. Enrofloxacin is used sparingly, in only about 1% of the total broiler production in 2000 of about 8.1 billion birds. The degree to which such limited usage might or might not affect the prevalence of fluoroquinolone-resistant infections in humans is ignored by FDA's formulation of the issue but is encompassed in Bayer's. Moreover, it is undisputed that U.S. per capita chicken consumption has increased from 1996 (the year enrofloxacin was approved) to 2000, while campylobacteriosis incidence rates have simultaneously decreased. FDA's formulation of the issue merely asks whether the transfer *can* happen, while Bayer's goes further and asks whether an unexpected transfer *is* happening and, if it is, whether this fact matters.

Subissue A (3)

This subissue now reads as follows:

> 3. Whether fluoroquinolone-resistant *Campylobacter* infections in humans have the potential to adversely affect human health?

Bayer Proposed Subissue A (3)

Bayer proposes that this subissue be rephrased as follows:

> 3. Whether CVM has presented new evidence that fluoroquinolone-resistant *Campylobacter* infections in humans caused by the use of enrofloxacin in chickens pose a greater potential hazard to public health than was anticipated at the time the drug was approved.

Subissue A (3) is flawed for the same reasons as described above. First, the subissue must address FDA's burden to show "new evidence." Second, FDA must produce evidence of a potential human health hazard beyond what was anticipated when enrofloxacin was approved.

The D.C. Circuit has emphasized the statutory directive that "[t]he Secretary, or Commissioner, may withdraw the approval if this 'new evidence . . . evaluated together with the evidence available . . . when the application was approved shows that such drug is not shown to be safe for use. . ." *Hess & Clark v. FDA*, 495 F.2d 975, 992 (D.C. Cir. 1974) (ellipses in original) (quoting 21 U.S.C. § 360b(e)(1)(B)). The court explained that "[t]his statute plainly places on the FDA an initial burden to adduce the 'new evidence' and what that new evidence 'shows.'" *Id.* The court went on to note that it is implicit in the statute that FDA must produce some evidence of the relationship between the drug and safety that warrants requiring the manufacturer to show that the drug is safe. *Id.* at 993. The crux of this holding is that there must be new evidence demonstrating that a potential hazard to human health exists that was not understood at the time the drug was approved. The potential hazard cannot be merely theoretical but must be such that it raises a serious question about the safety of enrofloxacin for use in chickens and turkeys.

Campylobacteriosis has been well known and understood as a major food-borne illness causing gastroenteritis since the 1980s, long before the approval of enrofloxacin in October 1996. *Campylobacter jejuni*, the organism believed responsible for 99% of all campylobacteriosis cases, causes an illness characterized by diarrhea, generally lasting 7 to 10 days, fever, abdominal pain, nausea, headache and muscle pain. Campylobacteriosis is almost always a self-limiting disease regardless of whether it is caused by a resistant or

susceptible *Campylobacter jejuni*. Significant complications of campylobacteriosis, such as Guillain-Barre syndrome have long been understood as extremely rare and frequently following asymptomatic infections, where there would no reason to prescribe an antibiotic. No protective effect of antibiotic treatment in acute campylobacteriosis on the development of complications has been demonstrated nor has the susceptibility of *Campylobacter jejuni* been related to the frequency of complications. The increased potential seriousness of campylobacteriosis in immune-compromised individuals such as chemotherapy patients, organ transplant patients and HIV-AIDS patients has also been well-recognized for many years before enrofloxacin approval for use in chickens and turkeys. In these patients the rapid development of fluoroquinolone-resistant *Campylobacter jejuni* from treatment with fluoroquinolones makes other classes of antibiotics preferable.

Similarly, treatment for campylobacteriosis, even of fluoroquinolone-resistant infections, has also been well understood medically, long before the approval of enrofloxacin for use in chickens and turkeys. The vast majority of people with campylobacteriosis do not seek medical care, and for the small numbers who do seek medical treatment antibiotics are either unnecessary or not indicated. The Centers for Disease Control and Prevention ("CDC") and FDA agree most infections are not even treated with antibiotics. In fact, fluoroquinolones have not been approved and are contraindicated for use in children; 27.5% of all *Campylobacter* infections occur in infants and an undetermined number of infections occur in older children. For the small percentage of persons for whom antibiotic treatment is indicated, antibiotics including fluoroquinolones may be an effective treatment, if treatment is commenced early, and data

suggest that fluoroquinolones may remain an effective clinical treatment even when the *Campylobacter jejuni* is determined to be resistant to fluoroquinolones by *in vitro* testing. Macrolides, an alternative class of antibiotics, are the preferred treatment for campylobacteriosis and are an alternative treatment for an infection that is clinically resistant to treatment with fluoroquinolones.

Accordingly, it is not sufficient for CVM merely to demonstrate that a potential for adverse impact on human health exists. Such a potential was clearly recognized well before enrofloxacin was approved. What CVM must demonstrate is that there is new evidence that raises a serious question, not a theoretical one, about a human health hazard from the use of enrofloxacin in chickens and turkeys.

The issue should be reformulated to require new evidence showing that there is a potential human health hazard not understood when enrofloxacin was approved.

II. FDA's PROPOSED ISSUES FAIL TO CONSIDER AN ASSESSMENT OF THE BENEFITS AND RISKS OF ENROFLOXACIN, INCLUDING THOSE UNDER SOME ALTERNATIVE PATTERN OF RESTRICTED USE.

Issue B

This issue now reads as follows:

> B. Whether the use of enrofloxacin under the approved conditions of use in poultry has been shown to be safe.

Proposed Issue B (1)

Bayer proposes that the statement of issues be enlarged to include the following:

> B. If such new evidence has been shown,
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> 1. Whether the benefits of continued enrofloxacin use in chickens under the current recommended or suggested conditions of use in the labeling or under some alternative pattern of restricted use outweigh the risks/costs of such continued use, such that enrofloxacin is safe. This

> analysis will include consideration of impacts on (a) human health, (b) animal health, (c) the environment, and (d) the economy . . . .

The issues as currently drafted by FDA unacceptably fail to consider the benefits and the risks of enrofloxacin, which is an essential step in determining whether a drug is "safe." Bayer submits that Issue B (1) should be added to the issues for hearing so that this crucial analysis is included.

As long ago as 1974, the D.C. Circuit recognized that consideration of the risks versus the benefits of a drug is an essential consideration in determining whether the drug will be safe when used as approved. The court recognized that:

> The typical issue for the FDA is not the absolute safety of a drug. Most drugs are unsafe in some degree. Rather, the issue for FDA is whether to allow sale of the drug, usually under specific restrictions. *Resolution of this issue inevitably means calculating whether the benefits which the drug produces outweigh the costs of its restricted use.*

Hess & Clark, 495 F.2d at 993-94 (emphasis added); *see also Stauber v. Shalala*, 895 F. Supp. 1178, 1191 (W.D. Wis. 1995) ("[U]nder the Food, Drug, and Cosmetic Act, neither the sponsors of new animal drugs nor the FDA is held to a 'zero risk' standard.").

While FDA has maintained in the past that it is not permitted by the statute to conduct such an analysis, the D.C. Circuit has emphatically rejected this position, noting that "[t]he language quoted above was not dictum. Rather it expressly set forth one of the issues to be considered at the hearing. Whatever the merits of the Commissioner's arguments on this point may be, we are bound by the holding of the *Hess & Clark* court until we are instructed otherwise by the Supreme Court or an *en banc* decision of this court." *Rhone-Poulenc, Inc. v. FDA*, 636 F.2d 750, 754 (D.C. Cir. 1980).

Additionally, the Supreme Court recently noted that the FDCA "generally requires FDA to prevent the marketing of any drug or device where the 'potential for inflicting death or physical injury is *not* offset by the possibility of therapeutic benefit.'" *FDA v. Brown & Williamson Tobacco*, 529 U.S. 120, 134 (2000) (emphasis added) (quoting *United States v. Rutherford*, 442 U.S. 544, 556 (1979)). The Court noted that FDA "may clearly regulate many 'dangerous' products without banning them. Indeed, virtually every drug or device poses dangers under certain conditions." *Id.* at 142.

Hence, consideration of the relative risks and benefits of enrofloxacin, including consideration of mitigation measures, is vital in FDA's analysis of whether the drug is safe under the approved conditions of use in chickens and turkeys. FDA's Issue B, however, merely asks whether "the use of enrofloxacin under the approved conditions of use in poultry has been shown to be safe." 67 Fed. Reg. at 7701. The issue as framed is vague as to what FDA wishes to have considered in determining "safety." Therefore, Bayer moves that the issues be reformulated so as to clarify that this issue must include an assessment of the risks and benefits of continued use of enrofloxacin.

Under relevant D.C. Circuit precedent, the issues for hearing must include an evaluation of risks and benefits to human health, animal health, the environment, and the economy. Such an evaluation is more than a mere academic exercise. Bayer will submit evidence that use of enrofloxacin in chickens and turkeys is a benefit to human health and that human health can be adversely impacted by the withdrawal of enrofloxacin due, for example, to increased contamination of chicken carcasses arising from processing of chicken flocks with air sacculitis disease absent an effective treatment. Moreover, Bayer will submit evidence that animal health will decrease and animal suffering will increase

without enrofloxacin. Increased mortality will result in an adverse environmental impact due to disposal issues as well as the need to increase production head count capacity to account for chickens no longer able to be saved by enrofloxacin treatment. Finally, Bayer will demonstrate economic harm to the chicken broiler industry well in excess of $100 million annually and to the turkey industry also well in excess of $100 million annually if enrofloxacin is removed from the market.

Bayer's subissue B (1) also makes explicit that consideration must be given to restrictions on use that would render withdrawal unnecessary, even if a safety problem were demonstrated with regard to enrofloxacin. The *Hess & Clark* court specifically noted that FDA typically imposes conditions of use that are calculated to limit potential risk of harm. *Hess & Clark*, 495 F.2d at 994 & n.60. Consideration of the general safety of enrofloxacin therefore must take into account possible alternative patterns of restricted use that would eliminate or mitigate potential risks. Bayer submits that mitigation measures (short of withdrawal of enrofloxacin) exist that, if put into place, could reduce even further any potential risk of fluoroquinolone-resistant *Campylobacter* transmission to humans while keeping enrofloxacin available to safeguard animal health. Therefore, potential mitigation factors must be examined prior to any withdrawal, and Issue B (1) should be revised to include evidence on potential mitigation measures.

III. THE SAFETY OF ENROFLOXACIN SHOULD BE ASSESSED SEPARATELY FOR CHICKENS AND FOR TURKEYS.

Bayer Proposed Subissues A (4), (5), (6) & B (2)

Bayer proposes that the statement of issues be modified to separate the issues of the safety of enrofloxacin for chickens and turkeys as follows:

4. Whether CVM has presented new evidence that the use of enrofloxacin in turkeys causes significant fluoroquinolone-resistant *Campylobacter* spp. in turkey meat consumed by humans;

5. Whether CVM has presented new evidence that fluoroquinolone-resistant *Campylobacter* spp. in turkeys caused by the use of enrofloxacin in turkeys are transferred to humans and are a significant cause of fluoroquinolone-resistant *Campylobacter* infections in humans; and

6. Whether CVM has presented new evidence that fluoroquinolone-resistant *Campylobacter* infections in humans caused by the use of enrofloxacin in turkeys pose a greater potential hazard to public health than was anticipated when the drug was approved.

B. If such new evidence has been shown,

* * *

2. Whether the benefits of continued enrofloxacin use in turkeys under the current recommended or suggested conditions of use in the labeling or under some alternative pattern of restricted use outweigh the risks/costs of such continued use, such that enrofloxacin is safe. This analysis will include consideration of impacts on (a) human health, (b) animal health, (c) the environment, and (d) the economy.

FDA's issues for hearing improperly collapse the use of enrofloxacin in chickens and turkeys under the single umbrella of "poultry." However, enrofloxacin is not approved for use in "poultry," but rather is separately labeled for specific use in chickens and turkeys. Because a proper analysis would require consideration of the safety of enrofloxacin separately for chickens and for turkeys, the issues for hearing should be reformed.

As is noted above, the FDCA provides that approval for a new animal drug shall be withdrawn if the Secretary of Health and Human Services finds

> [t]hat new evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to

> the secretary when the application was approved, *shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved* . . . .

21 U.S.C. § 360b(e)(1)(B) (emphasis added). Enrofloxacin has been approved for the control of mortality in chickens associated with *E. coli* organisms, as well as for the control of mortality in turkeys associated with *E. coli* and *Pasteurella multocida* organisms. The drug sponsor, Bayer, was required by FDA to submit data separately demonstrating in chicken and turkey the safety and efficacy of enrofloxacin. If enrofloxacin were not shown to be safe in chickens, there would be no reason to revoke the approval for its use in turkeys unless it was also not shown to be safe for that use.

Some of the differences between chickens and turkeys, and especially the differences in how they are used, are clear. Chickens and turkeys are raised differently and processed differently. For example, turkey houses are cleaned out more frequently and there is routine sanitation of turkey live-haul trailers. Turkeys are scalded at higher temperatures, are eviscerated manually and, due to a larger body mass, have extended chilling times compared to chickens. Each of these factors can have an impact on bacterial loads which are different compared to chickens. Additionally, far more chickens are grown, and consumed by humans, than turkeys. Substantially more raw chicken is sold to consumers for cooking and consumption at home, or to restaurants, than is the case with turkey. Not only is a larger *amount* of raw chicken sold to the end user, a higher *percentage* of all chicken consumed is sold raw than is the case with turkey. A substantial amount of turkey is commercially processed and pre-cooked for use in, for example, packaged lunch meat. Moreover, even the species of bacteria in question differs—*Campylobacter jejuni* is more common in chickens, while *Campylobacter coli* is more

common in turkeys. As previously noted, 99% of all cases of campylobacteriosis are believed to be caused by *Campylobacter jejuni*. Notwithstanding that each of these factors could affect development of fluoroquinolone-resistant *Campylobacter*, transmission rate to people and medical outcome, FDA proposes to introduce no evidence on this matter.

FDA's "findings" in the NOOH relate entirely to chickens. The NOOH cites no evidence whatsoever relating to turkeys. Nevertheless, FDA seeks to ban the use of enrofloxacin in *all* poultry. *See* 67 Fed. Reg. at 7701 (defining issues for hearing as including "[w]hether the use of enrofloxacin under the approved conditions of use in poultry has been shown to be safe"). If FDA wishes to reconsider the use of enrofloxacin in turkeys, it will be required to meet the same standards described above for chicken—i.e., it must produce new evidence that enrofloxacin is not safe for use under the approved conditions of use in turkey. Under FDA's formulation of the issues, however, it would be sufficient for FDA to present evidence relating *either* to chickens *or* to turkeys and then to claim that this evidence relates to *all* poultry. FDA should not be permitted to avoid its burden of proof in this manner.

Normally, sponsors seeking approval of a new animal drug for use in a major species are not permitted to use data extrapolation from another species—i.e., a showing that the drug is "safe" in one species does not then extend to cover other species as well. Such was the case for the approval of enrofloxacin for chickens and turkeys. The necessary implication of this requirement is that one cannot prove the safety of a drug in a given species without evidence specific to that species. Thus, under FDA's regulatory scheme, it is apparent that species are considered to differ in some fundamental way. Perhaps the two species are colonized by different bacteria which may affect people

differently, perhaps the two species have different incidences of illness, or perhaps the two species metabolize a drug differently; in all of these cases, the difference may well translate into different rates of resistance in bacteria, different rates of transfer of the bacteria to people and different effects on humans consuming the animal in question. Perhaps the two species have differences in processing, distribution and consumption, such that a risk unacceptable in one will be acceptable in the other. Whatever the particular concern in a given case, the regulatory scheme recognizes that the differences between species are important enough to require specific evidence of safety in each species in which a drug will be used.

Even if the use of enrofloxacin in chickens is determined to have some adverse effect on human health, it does not necessarily follow that the same is true of the use of enrofloxacin in turkeys. FDA proposes to address *none* of these issues, yet all of them are relevant. To name but a few significant questions: Do the two species of *Campylobacter* produce the same effects in humans? What percentage of *Campylobacter* infections can be traced to contaminated chickens, what percentage can be traced to contaminated turkeys, and are the numbers significant enough to pose a real problem?

In order for FDA to carry its initial burden of proof, it should be required to produce new evidence that raises serious questions about the safety of enrofloxacin as used in chickens and also as used in turkeys. To allow FDA merely to impute evidence about chickens to turkeys would violate the regulatory scheme that requires proof of a drug's safety in each species. Accordingly, the issues for hearing should be reformulated so that chickens and turkeys are addressed separately, thus clarifying that (1) enrofloxacin has

been approved for use in both species and (2) FDA must carry its burden of proof as to both species.

CONCLUSION

For the foregoing reasons, Bayer Corporation requests that the Commissioner's proposed issues be deleted and that the issues set forth herein be substituted in their stead.

Respectfully submitted,

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CERTIFICATE OF SERVICE

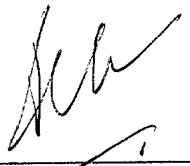
I hereby certify that a copy of Respondent's Bayer Corporation's Motion to Reformulate Issues for Hearing was mailed this 15th day of April, 2002, via first-class mail, postage pre-paid to:

Kent D. McClure
Animal Health Institute
1325 G Street, N.W., Suite 700
Washington, D.C. 20005

Brian Jensen
Royal Danish Embassy
Food, Agriculture and Fisheries Division
3200 Whitehaven Street, N.W.
Washington, D.C. 20008

I hereby certify that a copy of Respondent's Bayer Corporation's Motion to Reformulate Issues for Hearing was e-mailed and also mailed, postage pre-paid, this 15th day of April, 2002 to:

Nadine R. Steinberg, Esquire
Food and Drug Administration
Office of General Counsel (CGF-1)
5600 Fischers Lane, Room 7-77
Rockville, MD 20857



Robert B. Nicholas

UNITED STATES OF AMERICA
BEFORE THE FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

In the Matter of:

Enrofloxacin for Poultry:
Withdrawal of Approval of
New Animal Drug Application
NADA 140-828

FDA DOCKET: 00N-1571

ORDER

UPON CONSIDERATION of the Motion of Bayer Corporation to Reformulate the Issues for Hearing, any response thereto, and the Notice of Hearing dated February 13, 2002, and

IT APPEARING that judicial precedent (specifically *Hess & Clark v. FDA*, 495 F.2d 975 (D.C. Cir. 1974) and *Rhone-Poulenc, Inc. v. FDA*, 636 F.2d 750, 754 (D.C. Cir. 1980)) and a strict interpretation of 21 U.S.C. § 360b(e)(1)(B) require reformulation of the issues as set forth in the Notice of Hearing (67 Fed. Reg. 7700, 7701), it is hereby

ORDERED that the hearing issues be, and they hereby are, modified to read as follows:

> Whether new evidence shows that enrofloxacin is not now shown to be safe for use under the conditions of use upon which the application was approved. This issue includes:
>
> A. Whether CVM has presented new evidence that raises serious questions about the safety of enrofloxacin. Specifically:

1. Whether CVM has presented new evidence that the use of enrofloxacin in chickens causes significant fluoroquinolone-resistant Campylobacter spp. in chicken meat consumed by humans;

2. Whether CVM has presented new evidence that fluoroquinolone-resistant Campylobacter spp. in chickens caused by the use of enrofloxacin in chickens are transferred to humans and are a significant cause of fluoroquinolone-resistant Campylobacter infections in humans; and

3. Whether CVM has presented new evidence that fluoroquinolone-resistant Campylobacter infections in humans caused by the use of enrofloxacin in chickens pose a greater potential hazard to public health than was anticipated when the drug was approved.

4. Whether CVM has presented new evidence that the use of enrofloxacin in turkeys causes significant fluoroquinolone-resistant Campylobacter spp. in turkey meat consumed by humans;

5. Whether CVM has presented new evidence that fluoroquinolone-resistant Campylobacter spp. in turkeys caused by the use of enrofloxacin in turkeys are transferred to humans and are a significant cause of fluoroquinolone-resistant Campylobacter infections in humans; and

6. Whether CVM has presented new evidence that fluoroquinolone-resistant Campylobacter infections in humans caused by the use of enrofloxacin in turkeys pose a greater potential hazard to public health than was anticipated when the drug was approved.

B. If such new evidence has been shown,

1. Whether the benefits of continued enrofloxacin use in chickens under the current recommended or suggested conditions of use in the labeling or under some alternative pattern of restricted use outweigh the risks/costs of such continued use, such that enrofloxacin is safe. This analysis will include consideration of impacts on (a) human health, (b) animal health, (c) the environment, and (d) the economy; and

2. Whether the benefits of continued enrofloxacin use in turkeys under the current recommended or suggested conditions of use in the labeling or under some alternative pattern of restricted use outweigh the risks/costs of such continued use, such that enrofloxacin is safe. This analysis will include consideration of impacts on (a) human health, (b) animal health, (c) the environment, and (d) the economy.

DATED this the ___ day of April, 2002.

Daniel J. Davidson
Administrative Law Judge